REMARKS

Applicants respectfully request entry of the amendments hereinabove and reconsideration of the Office Action mailed on May 29, 2003 (for the parent application) and allowance of the application.

Applicants and their Attorneys A. Dean Olson and Martha G. Munchhof wish to express their gratitude to Examiner Deepak R. Rao for the courteous interview granted to A. Dean Olson and Martha G. Munchhof on July 22, 2004.

As a preliminary manner, Applicants have made reference to a number of U.S. Patents in their comments herein. Since these are easily available to the Examiner, Applicants have not included copies thereof. Should the Examiner like paper copies, Applicants are more than willing to supply such copies. Please contact the Applicants' attorney, A. Dean Olson (e.g., 860-441-4904).

Applicants have herein amended claims 1-18 in accordance with the restriction requirement drawn to Formula I compounds wherein ring A contains one nitrogen (consequently claim 2 was cancelled as redundant). Applicants note that they have included pyridine rings and N-oxide rings in the claims.

Applicants have also added new claims 19-22 directed to N-methyl-N-({3-[3-methyl-4-(methylsulfanyl)phenoxy]-4-pyridinyl}-methyl)amine and N-methyl-N-({3-[4-(methylsulfanyl)phenoxy]-4-pyridinyl}-methyl)amine and their tartrate salts. Support for such compounds may be found in Examples 38 and 35 respectively, and support for the salt may be found on page 7, line 17.

Claims 1-18 are rejected under 36 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation of compounds of formula (I) wherein ring A is a monocyclic ring having one nitrogen atom (i.e., pyridinyl) and for treating diseases such as hypertension, pain, etc., does not reasonably provide enablement for (a) the preparation of compounds wherein the two R^4 groups on ring A are linked together to form a fused ring (i.e., bicylcic compounds), etc.; (b) polymorph of compounds of formula I; and (c) for preventing the diseases embraced by the claims. The rejection states the specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention commersurate in scope with these claims.

The rejection also states that, in evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The rejection notes that the specification fails to enable the preparation of the claimed compounds wherein two R^4 are linked together with the interconnecting atoms to form a 5-7 membered fused ring with ring A. The rejection states from the schemes in the specification (at pages 10-16), it is clear that compounds of formula (II) is the essential starting materials to prepare the instantly claimed compounds. The rejection states that the compounds of formula (II) are in turn prepared from formula (III) or (V), however, in the discussion of the sources of these starting materials in pages 15-16, there is no disclosure of the sources of the starting materials required to prepare compounds wherein the R^4 groups together form a fused ring. The rejection states that all the examples are also towards monocyclic pyridinyl compounds.

Further, the rejection also states that the specification does not provide any explanation of what types of 'polymorphs' are intended, how these are made, etc. The rejection states that the existence, structure and the properties (e.g., stability, solubility, bioavailability, rate of dissolution, etc.) of polymorphs tend to be very unpredictable. The rejection states that in order to establish the most stable polymorphic form, each has to be characterized and screened individually using various analytical techniques such as X-ray diffraction, thermal analysis, particle morphology characterization, etc. The rejection states that in view of the lack of direction provided in the specification regarding the starting materials, the lack of working examples and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to

make the claimed compounds and therefore practice the invention. The rejection states that the starting material sources necessary to obtain the instant compounds must have been available as of the filing date in order to provide an enabling disclosure. See *In re Howarth,* 654 F.2d 103, 210 USPQ 689 (CCPA 1981); *Ex parte Moersch,* 104 USPQ 122 (POBA 1954).

The rejection notes that the method of claims 15-18 is not adequately enabled solely based on their ability to inhibit the uptake of serotonin by human serotonin transporters, provided in the specification. The rejection states that the instant claims cover 'disorders' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The rejection states that the use disclosed in the specification is a as pharmaceutical therapeutic agents having ability to inhibit the uptake of serotonin, useful to treat or prevent a large list of diseases, which include sexual disorders, neurodegenerative disorders, etc. The rejection states that the test procedure and assay for measuring the inhibitors potency is provided at pages 96-98 along with generalized IC_{50} values for some of the exemplified compounds, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. The rejection states that the disorders encompassed by the instant claims include sexual disorders, neurodegenerative diseases, etc., some of which have been proven to be extremely difficult to treat.

The rejection notes that a state of the art reference, Gainetdinov et al. expresses the uncertainties of pharmacological activities of drugs acting on monoamine transporters: "...important issues regarding the selectivity and mechanisms of action of these drugs remain unresolved", see the abstract. The rejection notes that Flatmark et al. (Annals N.Y. Acad. Sci. 2002) regarding pharmacology of Vesicular Monoamine Transporters, stated that "Although site-directed mutagenesis has identified transmembrane spanning domains and functionally important amino acid- and thus provided some information regarding structure and ligand binding sites in VMAT2 – the complete structure of this very hydrophobic intrinsic membrane protein is still a big challenge", see page 73.

The rejection states that there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey,* 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

The rejection also notes, further, claim 15 recites neurodegenerative diseases such as Alzheimer's disease, etc. which have been traditionally known to be very difficult to treat or even to identify with the mode of action. The rejection notes that in fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). The rejection states that for example, Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease." (pg. 1994).

The rejection states that the instant claims recite 'treatment or prevention', and therefore, the instant claim language embraces disorders not only for the treatment, but for "prevention" which is not remotely enabled. The rejection states that based on the serotonin re-uptake inhibitory activity, the instant compounds are disclosed to be useful in the "prevention" of sexual disorders, neurodegenerative disorders, etc., for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can be administered in order to have the 'preventive' effect. The rejection states that it is inconceivable from the *in vitro* data of a small number of representative compounds can be correlated to the 'prevention' of the various claimed disorders, such that the claimed compounds can not only treat but also "prevent" a myriad of diseases associated with the stated activity. The rejection states that further, there is no evidence on record

which demonstrates that the *in-vitro* screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of 'preventing'. The rejection states that such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study").

The rejection also states that part of the difficulty of developing drugs effective for preventing and of the medical conditions including sexual disorders, neurodegenerative disorders, etc. lies in the lack of understanding as to why people come down with these disorders and the numerous causes of these disorders.

The rejection notes that, thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. The rejection concludes that in view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to make and/or use the invention commensurate in scope with the claims.

Applicants traverse the rejection under under 35 U.S.C. 112, first paragraph of claims 1-18.

The rejection is based upon the proposition that undue experimentation would be required to practice the claimed inventions. All Wands factors must be considered "in determining whether a disclosure requires undue experimentation..." *In re Wands*, 8 USPQ2d 1400, at 1404 (Fed. Cir. 1988). Further, the issue on enablement is not whether experimentation, even a considerable amount of experimentation, might be required; the issue is whether the experiments required--in the <u>particular</u> art, with the skill of the art <u>in</u> <u>that</u> <u>field</u>

and with the extent and nature of the disclosure at issue--are "undue". *Id.* at 1404; see also MPEP 2164.01(a).

Enablement of R^4

The rejection specifically states the specification fails to enable the preparation of the claimed compounds wherein two R^4 are linked together with the interconnecting atoms to form a 5-7 membered fused ring with ring A-there are no Examples of such compounds.

Applicants submit that such compounds are enabled by for example, Example 104 (i.e., [2-(3,4-Dichlorophenoxy)-3-quinolinyl]-N-methylmethanamine; a quinoline) and Preparations 67 and 65. In addition, the skill in the art (e.g., bicyclic ring structures such as Formula III and V compounds are known) and the general discussions on page 16, lines 20-23 and page 14, lines 19-21 and 16-24 provide additional enablement.

However, in the interests of expediting prosecution Applicants have herein deleted such subject matter without waiver or prejudice against refilling such subject matter in a divisional application.

Enablement of Method of Prevention or Treatment Claims

Applicants submit that claims 15-18 are fully enabled.

However, in an effort to expedite prosecution Applicants have herein amended claims 15-18 to be directed to the treatment or prevention of premature ejaculation. Accordingly, claim 15 is amended to focus on premature ejaculation and claims 16-18 are cancelled. Such amendment is done without prejudice against the refilling and prosecution to grant of such additional subject matter.

Applicants submit that the term "prevent" is particularly appropriate and enabled for claim 15, as amended, since the condition is premature ejaculation. In fact, since the condition is premature ejaculation, for claim 15 to be rational the claim must include the term "prevent". While in a broad sense one is treating premature ejaculation, in another sense one is actually preventing the occurrence of a premature ejaculation. Restated, arguably a pharmaceutical compound prevents the occurrence of a premature ejaculation to be effective and

thus premature ejaculation is different from most other conditions/diseases where treatment may be sufficient. Again, for claim 15 to be rational the claim must include the term "prevent".

Applicants further submit that the use of SSRI's are documented for the treatment of premature ejaculation and thus the screening methods taught in the specification and the serotonin re-uptake inhibition (SRI) IC_{50} data provided in the specification (see pages 97-98) are recognized in the art as being reasonably predictive of success in the contemplated area of 'preventing' preventing premature ejaculation.

The literature (including patent literature) is replete with documentation for the nexus between selective serotonin reuptake inhibitors and premature ejaculation. For example, U.S. pat. nos. 6,150,376 and 5,998,405 disclose this nexus.

U.S. pat. no. 6,150,376 states

"For example, due to their selectivity for the serotonin transporter, the aza compounds according to structural formula (I) are particularly effective for the treatment of disorders involving the serotonergic neural system of the brain, such as eating disorders, depression, obsessive-compulsive disorder, panic disorders, alcoholism, pain, memory deficits and anxiety, and disorders linked to decreased transmission of serotonin in mammals, including Ganser's syndrome, migraine headache, bulimia, obesity, pre-menstrual syndrome or late luteal phase syndrome, alcoholism, tobacco abuse, panic disorder, depression, anxiety, post-traumatic syndrome, memory loss, dementia of aging, social phobia, attention deficit hyperactivity disorder, chronic fatigue syndrome, **premature ejaculation**, erectile difficult, anorexia nervosa, disorders of sleep, autism, mutism and trichotillomania."

U.S. pat. no. 5,998,405 states

"Therefore, the present invention also provides methods of treating several disorders linked to decreased neurotransmission of serotonin in mammals. Included among these disorders are depression and related disorders such as pseudodementia or Ganser's syndrome, migraine pain, bulimia, obesity, pre-menstrual syndrome or late luteal phase syndrome, alcoholism, tobacco abuse, panic disorder, anxiety, post- traumatic syndrome, memory loss, dementia of ageing, social phobia, attention deficit hyperactivity disorder, chronic

fatigue syndrome, **premature ejaculation,** erectile difficulty, anorexia nervosa, disorders of sleep, autism, mutism or trichotillomania."

Indeed, at least as far back as December 7, 1999 (well before Applicants' filing date) the impact of the serotonergic system on premature ejaculation was well recognized.

U.S. pat. no. 5,998,405 discloses

"The serotonergic neural system of the brain have been shown to influence a variety of physiologic functions, and the compounds of the present invention are predicted to have the ability to treat in mammals, including humans, a variety of disorders associated with this neural system, such as eating disorders, depression, obsessive compulsive disorders, panic disorders, alcoholism, pain, memory deficits and anxiety. Therefore, the present invention also provides methods of treating several disorders linked to decreased neurotransmission of serotonin in mammals. Included among these disorders are depression and related disorders such as pseudodementia or Ganser's syndrome, migraine pain, bulimia, obesity, pre-menstrual syndrome or late luteal phase syndrome, alcoholism, tobacco abuse, panic disorder, anxiety, post-traumatic syndrome, memory loss, dementia of ageing, social phobia, attention deficit hyperactivity disorder, chronic fatigue syndrome, **premature ejaculation,** erectile difficulty, anorexia nervosa, disorders of sleep, autism, mutism or trichotillomania."

In particular, U.S. pat. no. 6,228,864 teaches "It has now been discovered that administration of various serotonin agonists and antagonists is quite effective in the treatment of **premature ejaculation,** and addresses a number of the above-noted deficiencies in the art."

Also, U.S. pat. no. 6,667,322 teaches

"Hence the compounds of this invention are combined serotonin reuptake inhibitors/5HT (1A)agonists and are useful for the treatment of depression and other conditions related to or affected by the reuptake of serotonin and by the serotonin 1A receptor such as, depression (including but not limited to major depressive disorder, childhood depression and dysthymia), anxiety, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder (also known as pre-menstrual syndrome), attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, generalized anxiety disorder, obesity, eating disorders such as anorexia nervosa, bulimia nervosa, vasomotor flushing, cocaine and alcohol addition, sexual dysfunction (including **premature ejaculation)**, and related illnesses."

Enablement of Polymorphs

Applicants strongly submit that the term "polymorphs" is enabled.

Applicants note that the FDA's position is that polymorphs have the same active ingredient and are pharmaceutically equivalent. The FDA's decision on a citizen petition (i.e., Docket no. 01P-0428/CP1 &PSA1) involving Ceftin is instructive in the FDA's position on the approvability of polymorphs. The text of the full opinion may be found at the following website.

(http://www.fda.gov/ohrms/dockets/dailys/02/Feb02/021902/01p-0428_pdn0001_vol2.pdf)

"Different salts and esters of the same therapeutic moiety are regarded as different active ingredients because they have different chemical structures and, quite often, different adverse event profiles. FDA has long regarded chemical structure as being fundamental to the identity of an active ingredient. Consequently, FDA regards different salts and esters of the same therapeutic moiety as pharmaceutical alternatives rather than pharmaceutical equivalents. On the other hand, different polymorphs of an active ingredient have the same primary chemical structure (the differences are in physical form) and are considered pharmaceutical equivalents which means (among other things) that they are the same active ingredient(s). " (underlining added for emphasis, id. At pages 28-29)

Further, the FDA takes an even more extreme position with the general principle stated in the Orange Book that "the physical form of a drug substance is not relevant to a determination of whether a generic drug product has the same active ingredient as the reference listed drug for the purposes of generic drug approvals." (id. At page 27)

Further, Applicants note that the FDA's position is that polymorphs are pharmaceutically equivalent.

"FDA states in the *Orange Book* that the Agency considers drug products containing different polymorphs of the same drug substance, as well as products containing anhydrous and hydrated versions of the same substance, to be pharmaceutically equivalent. [34] *Orange Book (21st ed.) at xvi (2001).* The Orange Book describes pharmaceutical equivalents as, among other things, containing the same active ingredient(s). Therefore, FDA regards different polymorphs of a drug substance as the same active ingredient." (id. At page 11)

Accordingly, the FDA states

"Generally, a difference in the physical form of an active ingredient in the generic drug product from the physical form of the active ingredient in the reference listed drug, including a difference in the crystalline structure of the active ingredient, does not bar the approval of a proposed generic drug product." (id. At page 2-3.)

While the FDA acknowledges that differences in the physical form may impact bioequivalence it analogizes such differences to particle size that does not impact pharmaceutical equivalency.

"However, this difference in bioequivalence would not mean that the generic and reference listed drug products would not be the "same". In this sense, differences in the physical form of an active ingredient are similar to differences in the particle size of a drug substance, which do not result in differences in the identity of active ingredients but which can produce differences in solubility rate, dissolution behavior, and bioavailability." (id at page 12)

The rejection states that "the specification does not provide any explanation of what types of "polymorphs" are intended, how these are made, etc. The rejection states that the existence, structure and the properties (e.g., stability, solubility, bioavailability, rate of dissolution etc.) of polymorphs tend to be very unpredictable."

Applicants submit that the unpredictability of the art is not sufficient to support lack of enablement. An analogous situation existed in In Re Wands (cited in the rejection as the seminal case on enablement) in which claims to the identification of monoclonal antibodies that would have a high affinity for a hepatitis antigen were found as enabled. In In Re Wands the exact chemical structure of the desired antibodies, how many of the desired antibodies would exist and in fact whether any more of the antibodies could be found was not certain. Again, the court held that the claims in In Re Wands were enabled even in the face of such "unpredictability".

In In Re Wands the court stated that "Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired

antibody." Similarly, Applicants submit that practitioners of the polymorph art are prepared to screen for polymorphs and the discussion of such screening in the patent and scientific references provided below demonstrates that this is within the standard skill in the art.

Also, by analogy In Re Wands states "this process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics." Clearly, while such experiments were multi-step and required considerable work, such work was not a bar to the holding that the claims were enabled.

By analogy, Applicants submit that the screening for polymorphs, while requiring some work (typically standard simple one-step crystallizations followed by routine characterization-such is hardly undue experimentation), should not be a bar to the holding that Applicants' claims are enabled. In fact, such "work" is far less than the work (i.e., immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics) required (and held enabled) in the In Re Wands case.

Thus, under the holding of In Re Wands, even assuming as the Examiner submits "the existence, structure and the properties (e.g., stability, solubility, bioavailability, rate of dissolution etc.) of polymorphs tend to be very unpredictable (as stated in the rejection) " such is not sufficient for lack of enablement by analogy to In Re Wands.

Also, the law is emphatic that (1) an applications's sufficiency under section 112 , first paragraph, must be judged as of its filing date; and (2) an application need not teach, and preferably omits, that which is well known in the art. See, for example, In The Matter Of The Application Of John Paul Hogan And Robert L. Banks, 194 U.S.P.Q. (BNA) 527 (CCPA 1977) as to point (1) and Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (at 94) (Fed. Cir. 1986) as to point (2).

Further, the case cited by the Examiner, In Re Howarth, is particularly applicable to the point (2):

"The court recognizes that part of the skills of such persons includes not only basic knowledge of the particular to which the invention pertains but also the knowledge of where to search out information. Well known textbooks in English are obvious research materials. Similarly, public records concerning U.S. patents are likely to be checked, and information therein is reasonably accessible in view of the published abstracts and our classification system. Thus, U.S. patents are considered pertinent evidence of what is likely to be known by persons of ordinary skill in the art." Id. At 690

Further, the issue on enablement is not whether experimentation, even a considerable amount of experimentation, might be required; the issue is whether the experiments required--in the particular art, with the skill of the art in that field and with the extent and nature of the disclosure at issue--are "undue". *Id.* at 1404; see also MPEP 2164.01(a). Further, "[i]t is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *Ex parte Obukowicz,* 27 USPQ2d 1063, 1067 (Bd. Pat. App. & Interf. 1992)

Applicants will discuss below several factors which support enablement in this case. Applicants submit that when these factors are considered, including the specific teachings in the specification and the level of skill in this art, as evidenced by the patents and publications cited herein, the term polymorphs is fully enabled, and this application should be promptly passed to issue.

In summary, one skilled in the art, with Applicants' teachings before him and with due regard to the knowledge in the art as of Applicants' effective filing date, would be able to practice the full scope of claim 1 at least because:

(1) the specification disclosed Examples of useful Formula I polymorphs and the specification teaches procedures to prepare the exemplary polymorphs

(2) the art taught the preparation and characterization of polymorphs as of Applicants' filing date

(3) other U.S. patents having similar claims are regularly granted.

APPLICANTS' SPECIFICATION

Applicants' specification plainly taught one skilled in the art that the invention, in its broader aspects, included "polymorphs thereof " (page 1, line 17; page 18, lines 6-8, lines 10-12, page 21, lines 5-7 etc.). Thus, in the first instance, the inventors clearly explained their invention in terms that encompassed claim 1 currently at issue.

Further, Applicants taught in Examples 35 and 38 exemplary polymorphs and their preparation. According to the procedure as detailed in Example 34 a simple "work up" by addition of a small amount of a non-solvent was used. Again, this is hardly undue experimentation.

While the characterization data for the hydrochloride amine salts of examples 35 and 38 do not specifically recite that they are crystalline, that is not necessary since one practicing the Examples would inherently produce the crystalline material. If desired, routine microscopy can be used to characterize the material as crystalline.

It is also likely that many of the other Examples produced crystalline material since they are also primary amine hydrochloride salts having similar structure and properties to examples 35 and 38 and they were similarly isolated as solids and "worked up" by trituration with a solvent (e.g., ether). However, these other solid materials were not conclusively examined for crystallinity (e.g., by microscopy).

Further, while the rejection states that "In view of the lack of direction provided in the specification regarding the starting materials " the specification is lacking in enablement, Applicants strongly submit that the starting materials are disclosed. First, Applicants have herein amended the claims to delete those compounds wherein A is a bicyclic structure (see R^4 enablement section). Second, each Example whether a crystal or not is a starting material for accessing further polymorphs. Second, Applicant has provided the enablement for the starting materials for the claimed compounds and this has not been

challenged (with the exception of the bicyclic Ring A compounds discussed above).

POLYMORPH ISOLATION AND CHARACTERIZATION WAS WELL KNOWN AS OF APPLICANTS' FILING DATE

Again, an application need not teach, and preferably omits, that which is well known in the art. See, for example, Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (at 94) (Fed. Cir. 1986)

There are numerous scientific publications and patents known as of the effective filing date of the instant application which disclose polymorph preparation (again, these are simple one-step crystallizations (in comparison to the multi-step preparations in In Re Wands) and characterization.

The scientific literature was replete with knowledge regarding polymorphs and their formation as evidenced by the following exemplary references known to those skilled in the art as of Applicants' filing date.

Thus, as early as 1990 Remington Pharmaceutical Sciences, (Eighteenth Edition, 1990) Chapter 75 PREFORMULATION, (enclosed) discusses polymorphs at length, and in particular, page 1440 states

"Preformulation usually includes rigorous studies to determine the presence of polymorphs in new drug substances being prepared for preliminary investigation in test animals. Some of the parameters routinely investigated are the number of polymorphs that exist, relative degree of stability of the various polymorphs, presence of a glassy state, stabilization of metastable forms, temperature stability ranges for each polymorph, solubilities, method of preparation of each form, effect of micronization or tableting and interaction with formulation ingredients.

The initial task of the preformulator is to determine whether or not the drug substance being evaluated exists in more than one crystalline form. The following procedures are usually followed to cause crystallization of a metastable form[3] *(Haleblian h, McCrone W: J Pharm Sci 58: 911, 1969)* :

1. Melt completely a small amount of the compound on a slide and observe the solidification between crossed polars. If, after spontaneous freezing, a transformation occurs spontaneously or can be induced by seeding or scratching, the compound probably exists in at least two polymorphic forms. It is

essential to prevent nucleation of the stable form by inducing supercooling. Supercooling can be induced by using a small sample size, holding the melt for approximately 30 sec about 10° above the melting point; carefully setting aside the compound without physical shock before observing it and rapid cooling of the compound.

2. Heat a sample of the compound on a hot stage and observe whether a solid-solid transformation occurs during heating.

3. Sublime a small amount of the compound and attempt to induce a transformation between the sublimate and the original sample by missing polymorphs, the more stable one will be more insoluble and will grow at the expense of the more soluble metastable form. This process will continue until the metastable form is transformed completely to the stable form. If the samples are not polymorphs, one may dissolve but the other will not grow. If the two are identical forms, nothing will occur.

4. Maintain an excess of the compound in a small amount of solvent held near the melting point of the compound. Isolate the suspended solid. Care should be taken to maintain the temperature during this step. Test the isolated material with an original sample using the procedure outlined in 3, above.

5. Recrystallize the compound from solution by shock-cooling, and observe a portion of the precipitated material suspended in a drop of the mother liquor. The drop then may be seeded with the original compound to check for solution-phase transformation. If the precipitate is a different polymorph, a solution-phase transformation should take place."

Further, the 1990 edition on page 1440 provides an overview of standard techniques for crystal identification including Microscopy, Hot-Stage Methods, X-Ray Powder Diffraction, Infrared Spectroscopy, Thermal Methods, and Dilatometry.

The 2000 edition Remington: The Science and Practice of Pharmacy, (Twentieth Edition, 2000) Chapter 38 PREFORMULATION (enclosed) clearly demonstrates the advance in the art as it takes a much more mathematical approach in light of the advances in the art. For example, page 718 states "The computational ability to link molecular structure with crystal packing has advanced to the point that polymorphic predictions are becoming more reliable for small molecules." It also discusses (at page 708) mathematical modeling of the intraconversion of polymorphs at different conditions e.g., temperature. Further, the 2000 edition on page 709-710 provides an overview of standard techniques for crystal identification including Hot stage microscope analysis,

Differential Scanning Calorimetry, Powder X-Ray Powder Diffraction, Single-crystal X-ray diffraction and Solid-state nuclear magnetic resonance (NMR). It also discusses constructing fluid-phase transformations as a function of temperature plots to identify the most stable form at low temperatures.

Thus, by 2000 well before Applicants' filing date the art had advanced to a certain theoretical level of polymorph understanding.

In addition, *Pharmaceutical Research*, vol. 12, No. 7, 1995 (enclosed) includes the Review "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations by Bryn, Stephen et al. This publication which was available as of the filing date of Applicants' application discusses a decision tree approach to identifying and characterizing pharmaceutical solids (e.g., polymorphs) and methods of preparing and characterizing different polymorphs. Applicants submit that an art that has advanced to decision tree analysis does not represent one that requires undue experimentation.

Finally, Solid State Chemical Inc. is a company that has existed since 1992 that performs standard "characterization and chemistry of solid materials" including screening for and characterization of polymorphs and it's website, http://www.ssci-inc.com/, details standard courses in pharmaceutical solids (e.g., polymorphs) that it has offered since prior to the filing date of this application. The company also offers a standard reference book that has been available since prior to Applicants' filing date (Solid-State Chemistry of Drugs 1999. Stephen R. Byrn, Ralph R. Pfeiffer, and Joseph G. Stowell). Much of this book is relevant to polymorphs, however, Applicant's note in particular Chapter 1.5 (enclosed) "HOW CRYSTALS FORM, pages 15-22" and Chapter 22.1 (enclosed) "CRYSTALLIZATION, pages 461-467".

A pertinent selection from chapter 1.5 is

Table 1.5 "Common Methods for the Production of Solids in the Pharmaceutical Industry". This Table lists for example, evaporation, cooling a solution, changing pH, salting out etc. Beyond the fact that these are presented as common methods one must take note of the simplicity of these methods.

Also, as stated above there are numerous patents that claim polymorphs. Consistent with In Re Wands statement "This is consistent with this court's recognition with respect to another patent application that methods for obtaining and screening monoclonal antibodies were well known in 1980." it is entirely appropriate to look to the patent literature for an acknowledgment of what is the skill in the art.

Presumably the granted U.S. patents that claim (in an analogous fashion) similar chemical genera and "polymorphs" thereof are fully enabled for teaching one with skill in the art with sufficient knowledge to prepare polymorphs. Attention is directed to the following exemplary patents:

5,919,782
5,889,032
5,889,025
5,801,173
5,760,054
6,159,966
6,130,214
6,114,526

Thus, procedures to evaluate polymorphs were not beyond the routine skill in the art and the principles of screening procedures had been taught in the art regarding both how to prepare and characterize such polymorphs.

In particular U.S. pat. no. 5,919,782 describes suitable procedures.

"Various polymorphs of compound of general formula (I) forming part of this invention may be prepared by crystallization of compound of formula (I) under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may

be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray data or such other techniques."

Also, U.S. pat. no. 6,001,845 describes the crystallization of phentolamine using "suitable or conventional crystallization procedures" thus acknowledging the skill in the art.

OTHER U.S. PATENTS WITH CLAIMS TO POLYMORPHS

The PTO has approved the issuance of patents claiming pharmaceutical compounds and polymorphs thereof. Thus, claim 1 presented by Applicants, is in a breadth and format which have been repeatedly accepted as entirely proper.

The following is an exemplary list of granted U.S. patents that claim genera of compounds including "polymorphs" of such compounds. These patents are all in class 546 (as is Applicants' compounds). Importantly, patents were granted with such claims as recently as January 13, 2004 (i.e., see claim 8 of U.S. pat. no. 6, 677,335) and December 9, 2003 (i.e., see claim 1 of U.S. pat. no. 6,660,756)

6,750,224
6,677,335
5,919,782
6,660,756
6,624,171
6,608,078
5,889,032
5,889,025
5,801,173
5,760,054
6,051,570

Applicants' claim 1 should be permitted, just as was approved in the above illustrative patents.

In light of this illustrative disclosure, Applicants clearly taught that (a) the invention was certain phenyl heterocyclyl ethers and "polymorphs" thereof and (b) described (inconjunction with the skill in the art) polymorphs and their preparation.

Consequently, even assuming that there is a low level of predictability in the chemical arts (as impliedly argued by the Examiner "The existence, structure and the properties (e.g., stability, solubility, bioavailability, rate of dissolution, etc.) of polymorphs tend to be very unpredictable" Applicants' disclosure in conjunction with the known skill in the art tells one how to practice the invention and how to carry out the full scope of the invention described in claim 1.

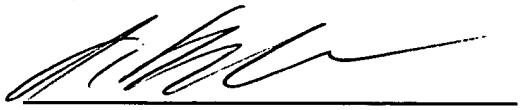
The experimentation employed here is not undue. This important application has enriched the art and claims commensurate with the importance and breadth of the described invention should be allowed.

Applicants enclose herewith an Information Disclosure Statement.

Applicants request allowance of the application.

Respectfully submitted,

Date: 12/14/2004



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